REMARKS

Claims 1-78 are pending. Claims 3-8 and 35-73 are withdrawn.

Rejection of Claims 1, 2, 9, 11-19, 22-28, and 76-78 Under 35 U.S.C. §102

The Office Action rejects claims 1, 2, 9, 11-19, 22-28, and 76-78 under §102 as being anticipated by Faulkner et al. The Office Action states that Faulkner et al. teaches the development of a chimeric vaccine comprising a 10 amino acid region of HA from influenza virus A/PR/8/38 linked to IL-2, and that Faulkner et al., thus, teaches all of the elements of the invention as claimed. Applicants disagree and traverse the rejection.

As recited in the claims, the first amino acid sequence of the fusion polypeptide must be able to bind carbohydrate. It is readily evident that the HA peptides taught by Faulkner et al. cannot do so. Aytay and Schulze (1991, J. Virology 65: 3022) teach that the carbohydrate binding domain of HA consists of a shallow pocket present on the distal end of the HA1 subunit. The specific sialic acid binding region has also been identified. Weis et al. (1988, Nature 333: 426) teach that the binding site is a depression, the bottom of which is formed by the phenolic hydroxyl of Tyr 98 and the aromatic ring of Trp 153, that Glu 190 and Leu 194 project down to form a short alpha-helix to define the rear of the site with His 183 and Thr 155, and that residues 134 to 138 form the 'right' side of the site and residues 224 to 228 form the 'left' side. Moreover, various mutagenesis studies have been carried out to determine residues in the binding pocket which are critical for SA binding (see, e.g., Nobusawa et al., 2000, Virology, 278:587; Martin et al., 1998, Virology 241:101; Nobusawa and Nakajima, 1988, Virology 167: 8; and Rogers et al., 1983, Nature 304: 76). It is thus known in the art that amino acids 98, 134-138, 153, 155, 183, 190, 194, and 224-228 of HA are critical for sialic acid binding.

The short HA peptide taught by Faulkner et al. has the sequence SFERFEIFPK and spans amino acid positions 110-119. Faulkner et al. also teaches a second HA peptide spanning positions 94-131. The peptides disclosed by Faulkner thus omit residues involved in and critical for carbohydrate binding. Thus, these peptides

could not bind carbohydrate, and neither Faulkner nor the Office Action provides any evidence that they can do so.

Furthermore, the instantly claimed vaccine composition does not consist solely of a fusion polypeptide; it ***further*** comprises an antigen bearing target. The language "further" clearly requires that the fusion polypeptide and the antigen bearing target be distinct from each other. Faulkner et al. does not teach a vaccine composition comprising the recited fusion polypeptide in combination with an antigen bearing target.

A rejection under 35 U.S.C. §102 cannot be sustained unless the cited prior art teaches each element of the claimed invention. Since Faulkner et al. fails to do so as set forth above, Applicants respectfully request that the rejection be withdrawn.

Rejection of Claims 10, 20, 21, 29-34, 74, and 75 Under 35 U.S.C. §103

The Office Action rejects claims 10, 20, 21, 29-34, 74, and 75 under §103(a) as being obvious over Faulkner et al. in view of Guillett et al., Robinson et al., Operschall et al., and Nobusawa et al. The Office Action states that it would have been obvious to include a linker in a fusion protein as taught by Guillett et al. and Robinson et al., and to substitute HA subtypes taught by Nobusawa et al. for the HA peptides taught by Faulkner et al. The Office Action further alleges that Operschall et al. would have provided motivation to produce the fusion protein recited in the claim, and that the references when combined teach each aspect of the instant invention.

Applicants disagree, and therefore traverse the rejection.

First, even if the references are combined, they do not provide all of the elements of the invention as claimed. The vaccine composition of the claimed invention must ***further*** comprise the recited fusion polypeptide, in addition to comprising an antigen bearing target. None of the references, including Faulkner et al. as set forth hereinabove, teaches the recited fusion polypeptide, and indeed none teaches any fusion polypeptide in a composition which further comprises an antigen bearing target. Thus, the references cannot be properly combined to support a rejection of the instant claims under 35 U.S.C. §103(a). Furthermore, there would have been no motivation to

combine, e.g., Faulkner et al's fusion protein with a distinct antigen bearing target, since that reference's goal was to generate an immune response to the HA peptide contained in the fusion, and there was no suggestion that the fusion protein as a whole should be used to heighten the response to an extrinsic, non-fused antigen.

In addition, with respect to substitution of the HA proteins taught by Operschall et al. and Nabusawa et al. for the non-carbohydrate-binding peptide taught by Faulkner et al., there would have been neither motivation nor a reasonable expectation of success. Faulkner et al. teaches that the cytokine moiety selectively targets the fusion construct to highly specialized dendritic cells after the construct is administered to a subject. It further teaches that this selective targeting increases uptake of the fusion protein, including the antigen, through specific binding to the cytokine receptor and subsequent receptor-mediated endocytosis.

Such a mechanism is possible in the constructs of Faulkner because the HA peptides, for which carbohydrate-binding HA protein would be substituted according to the Office Action, would not be expected to affect the cytokine's ability to reach and bind to the dendritic cells, which are being targeted to enhance the immune response to those very moieties, since as noted above, the HA domain taught by Faulkner et al. does not bind carbohydrate. **However**, carbohydrate-binding HA presents an altogether different situation because it binds efficiently sialic acid, which is present on the surface of most mammalian cells. Thus, a fusion polypeptide comprising a sialic acid binding moiety, e.g. hemagglutinin, would adsorb indiscriminately to cells at the site of administration or expression, most of which would not be dendritic cells. This would prevent the construct from reaching the dendritic cells, and would therefore interfere with the targeting and uptake taught by Faulkner et al. One of skill in the art would also reasonably expect that, even if one of the fusion protein molecules were to contact a dendritic cell by chance, the simultaneous binding to sialic acid might interfere with the cytokine receptor mediated events taught by Faulkner et al.

Thus, one of ordinary skill in the art would not have had a reasonable expectation of success in combining the cited references, and indeed would not have been at all motivated to do so.

It is well settled that the proposed modification to reach a finding of obviousness cannot render the prior art unsatisfactory for its intended purpose; if the modification would render the prior art unsatisfactory for its intended purpose, there can be no suggestion or motivation to make the proposed modification. MPEP §2143.01(V). In addition, if the proposed modification or combination of the prior art would change the principle of operation of the prior art being modified, then the teachings of the references are not sufficient to render the claims obvious. MPEP §2140.01(VI). In the instant case, as noted above, the principle of operation of Faulkner et al. is that the cytokine targets the construct to dendritic cells. To modify the teachings of Faulkner et al. to, instead, utilize a hemagglutinin moiety in a fusion protein to bind to carbohydrate (specifically, sialic acid) would completely alter the biological principles that are relied on by Faulkner et al. for the operativity of its teachings. In addition, as described above, to modify or combine the references as suggested by the Office Action would prevent the fusion constructs of Faulkner et al. from reaching the dendritic cells, and would therefore interfere with the targeting and uptake taught by Faulkner et al; that is, it would render the prior art unsatisfactory for its intended purpose, i.e. targeting of the construct to dendritic cells via cytokines.

Furthermore, Operschall et al. teach administration of plasmid DNA ***encoding*** proteins, which is fundamentally disparate from immunization with proteins and antigen bearing targets. It does not teach a fusion construct at all, even encoded by the DNA. Indeed, given the operativity of the plasmid vaccine, there would have been no motivation to take the additional steps of making the HA-GM-CSF chimeric gene and expressing the fusion protein.

The narrow teachings of Guillett et al. and Robinson et al. regarding linkers do not supply the teachings missing from the other references to support the rejection under §103.

In view of the above arguments, Applicants respectfully requests withdrawal of the rejection under 35 U.S.C. §103(a).

Rejection of claims 1, 9, 10, 12, and 74-78 Under 35 U.S.C. §112, First Paragraph

Claims 1, 9, 10, 12, and 74-78 are rejected under 35 U.S.C. §112, first paragraph because the specification allegedly does not provide adequate written description of the invention as claimed. Applicants disagree and traverse the rejection.

In the claimed invention, the recited fusion polypeptide comprises first and second portions with defined, limiting functions. With respect to the first amino acid sequence, the specification discloses a large, representative number (well over 500) of the recited moieties (e.g. paragraphs 0093-0134). Similarly, with respect to the second amino acid sequence, the specification teaches a representative number (well over 100) of examples (e.g. paragraphs 0142-0425). The specification also teaches assays that determine whether one molecule is a ligand for another (e.g. paragraphs 0442-452), and similar assays, e.g. competitive binding assays, are routine and well-known to those skilled in the art.

In addition, the specification teaches a representative number of antigens and antigen bearing targets (e.g. paragraphs 0005, 0041, 0074, 0428-0441, 0469-0475 [which also refers to 0536-0538]).

Thus, each of the recited elements of the claimed invention is illustrated by a representative number of examples, and is sufficiently described to evidence to one of skill in the art that Applicants were in possession of the full scope of such molecules at the time the instant application was filed. Furthermore, each element is defined by a functional characteristic which is easily discernible to one skilled in the art. Accordingly, Applicants submit that they have complied with the written description requirement and respectfully request that the rejection be withdrawn.

Rejection of Claims 1, 2, 9-34, and 74-78 Under 35 U.S.C. §112, Second Paragraph

Claims 1, 2, 9-34, and 74-78 are rejected under §112, second paragraph for alleged indefiniteness. The Office Action states that it is unclear what the term "antigen bearing target" means. Applicants traverse the rejection.

In connection with this rejection, Examiner requests clarification of the invention. Applicants believe that the claims are clear, but are pleased to provide further comment in an effort to facilitate prosecution.

The claimed vaccine composition comprises two distinct elements, as follows:

1) An antigen bearing target; and, "further",

2) A fusion polypeptide, the component sequences of which are delimited in the claims.

Without being bound by any mechanism, the antigen bearing target may be viewed as providing the antigen against which an immune response is to be elicited. The fusion polypeptide may be viewed as increasing or otherwise modifying the immune response to the antigen provided by the antigen bearing target, which again is separate from the fusion polypeptide. Unexpectedly, the carbohydrate binding ability of the fusion polypeptide is critical to the full adjuvant activity of the fusion polypeptide.

In the elected species, HA provides the carbohydrate-binding sequence of the fusion polypeptide; it is ***not*** the elected viral antigen, which is provided by the separate antigen bearing target (and which need not be HA). The fact that the carbohydrate-binding sequence (HA) of the fusion polypeptide is, in this embodiment, also from a viral protein is incidental.

The term "antigen bearing target" is specifically defined at paragraph 0005 of the specification. Further exemplification is provided, e.g., at paragraphs 0041, 0066, and 0074. "Antigen" is defined at paragraph 0006. Therefore, Applicants respectfully submit that the allegation of indefiniteness is inapposite, and request that the rejection be withdrawn.

Double Patenting

Claims 1, 11, 12, and 22-34 are provisionally rejected for being unpatentable over claims 1-3 and 9-13 of copending Application No. 10/666,833. Claims 1, 2, 9-34, and 74-78 are provisionally rejected for being unpatentable over claims 1, 8-33, and 73-77 of copending Application No. 10/667,166. Claims 1 and 22-34 are provisionally rejected for being unpatentable over claims 1-3 and 9-13 of copending Application No. 10/666,866. Claims 1, 2, 9-29, 31, 32, 34, 74, and 75 are provisionally rejected for being unpatentable over claims 1-22, 24, 25, 27, 67, and 68 of copending Application No. 10/666,871.

With respect to the foregoing rejections, upon notification of allowable subject matter in the instant case Applicants plan to timely file terminal disclaimers effective to obviate the double patenting rejections. Applicants nevertheless reserve the right to traverse any or all of these rejections at a later date.

The following rejections are all made in view of Faulkner et al.: Claims 1, 2, 9-29, 31, 32, 34, and 74-78 are provisionally rejected for being unpatentable over claims 1, 8-28, 30, 31, 33, and 73-77 of copending Application No. 10/666,834. Claims 1, 2, 9-29, 31, 32, 34, 74, and 75 are provisionally rejected for being unpatentable over claims 1-22, 24, 25, 27, 67, and 68 of copending Application No. 10/666,898. Claims 1, 2, 9-29, 31, 32, 34, 74, and 75 are provisionally rejected for being unpatentable over claims 1-22, 24, 25, 27, 67, and 68 of copending Application No. 10/666,895. In each instance, the Office Action relies on an allegation that Faulkner et al. teaches a fusion polypeptide recited in the claims of the copending applications. Applicants respectfully disagree and traverse the rejections.

Each of the following arguments is presented in greater detail hereinabove in rebutting the statute-based rejections. The HA peptides in the fusion polypeptides of Faulkner et al. do not bind to sialic acid or any carbohydrate. Such binding is an integral limitation in the copending claims. Indeed, inclusion of a sialic-acid binding HA would be expected to render Faulkner et al's fusion polypeptide inoperative. There would have been no motivation to replace the HA polypeptide of Faulkner with sialic-acid binding HA, and no expectation of success in doing so. Moreover, Faulkner et al.

does not teach a vaccine composition which comprises an antigen bearing target and ***further*** comprises a fusion polypeptide.

In view of the foregoing, Applicants respectfully request withdrawal of all double-patenting rejections which rest on Faulkner et al.

Applicants submit that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicants' attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

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